BIOCOMPATIBLE POLYMERIC DELIVERY SYSTEMS HAVING FUNCTIONAL GROUPS ATTACHED TO THE SURFACE THEREOF

This application claims the benefit of U.S. Provisional Application No. 20 60/139,950, filed on Jun. 18, 1999.

BACKGROUND

In recent years a number delivery systems comprised of a biocompatible polymer and a drug for treating a particular disease or condition have been produced. Polymeric drug delivery systems include implantable devices, such as stents, that are implanted into particular regions of the body for localized delivery of the drug. Polymeric drug delivery systems also include specific geometrics such as for example, microspheres, nanospheres, and cylinders that are injected through a needle into the body of the patient, e.g. into a muscle or the blood stream. The particles are injected into the blood stream for systemic delivery or delivery to a specific site. Targeted delivery to a specific site maximizes drug action and minimizes side effects. The ability to minimize side effects is especially important in cancer chemotherapy, vaccine delivery, and diagnostic imaging.

In order to target polymeric particles to a particular tissue or region of the body, it is necessary to include functional groups, such as ligands and antibodies, on the surface of the polymeric particle. Functional groups are also included on the surface of polymeric particle to avoid clearance by the reticuloendothelial system (RES) Without such groups, sufficient quantities of the particles may not reach the targeted tissue or site. In certain cases, bioactive molecules, such as peptide vaccines and genes, may also be attached to the surface of polymeric particles.

Attempts have been made to attach functional groups or bioactive molecules to the polymeric particle by modifying the biocompatible polymers themselves. The most successful methods that are currently employed involve covalently linking conjugatable or ligatable groups to the biocompatible polymer (e.g. to form a block copolymer) prior to formation of the polymeric particle. Such methods result in the formation of a modified polymer or copolymer which, unfortunately, does not have the same physical bulk properties as the unmodified polymer. Such methods are also expensive, inefficient, and time consuming.

Accordingly, it is desirable to have new methods of making biocompatible polymeric delivery systems that have functional groups, including conjugatable groups, on the surface thereof.

SUMMARY OF THE INVENTION

The present invention provides new methods for making biocompatible polymeric matrices, particularly polymeric particles, that have functional groups on the surface thereof. The method comprises: providing a biocompatible base polymer, preferably a biodegradeable base polymer; providing a surface-active, functional polymer, hereinafter referred to as an "SAFP"; entangling chains of the base polymer with chains of the SAFP, both of which are in a mobile state; and then de-mobilizing the base polymer chains to form a polymeric particle or matrix having a specific geometry, e.g. sheet. Advantageously, the present method does not involve copolymerization of the SAFP chains with the base polymer. The present method modifies only the surface of the polymeric particle or sheet and, thus, retains the bulk properties of the base polymer. The present method provides a polymeric delivery system which can be used to slowly release drugs. The present method is simple and efficient.

The present invention also provides a polymeric particle having functional groups on the surface thereof. The particles comprise a biocompatible base polymer and an SAFP. The SAFP comprised at least one interactive region for physically cross-linking with the base polymer, preferably a plurality of interactive regions, and at least one hydrophilic region, preferably a plurality of hydrophilic regions. The particles have a core region and an outer region having a an outer surface. The core region contains a plurality of the biocompatible base polymer chains, which preferably are formed from a biodegradeable and bioresorbable base polymer. The outer region of the particle contains a plurality of biocompatible base polymer chains and the interactive regions of the SAFP. Preferably, the interactive region or regions of the SAFP chains penetrate into the outer region of the particle and thus, become entangled or physically cross-linked with one chain or, preferably, multiple chains of the base polymer. The hydrophilic functional region or regions of the SAFP chains extend from the surface of the particle when the particle is placed in an aqueous solution.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a schematic representation of a method used to prepare microspheres and nanospheres composed of a base polymer and an SAFP.

FIG. **2** is a schematic representation of a method used to incorporate an SAFP into the outer region of a pre-formed polymeric microsphere or nanosphere.

FIG. **3**A is a scanning electron micrograph of poly (lactide-co-glycide) (PLGA) microspheres prepared from acetylated poly (L-lysine), AP-6; and

FIG. **3**B is a scanning electron micrograph of poly (lactide-co-glycide) (PLGA) microspheres prepared from acetylated poly (L-lysine).

FIG. **4** depicts the calibration curve of lysine residue determination on the surface of PLGA microspheres prepared from acetylated poly (L-lysine).

FIG. **5** shows the extent of retention of polylysine on PLGA microspheres prepared from acetylated poly (L-lysine).

FIG. **6** is a schematic diagram of possible configurations of the SAFP at an emulsion droplet surface.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method for making a polymeric matrix having functional groups on the surface thereof. The method comprises providing a base polymer; providing an SAFP; physically cross-linking chains of the SAFP with chains of the base polymer, and then de-mobilizing the base polymer chains to form a solid polymeric particle or porous or nonporous sheet of any moldable shape.

The base polymer is a biocompatible polymer. As used herein the term biocompatible refers to a polymer that is approved for use in the body by the Food and Drug Administration. Examples of biocompatible polymers are poly (ethylene-covinyl acetate), and silicone rubber cross linked to poly (dimethyl siloxan sulfoxide) and derivatives thereof. Preferably, the base polymer is biodegradeable and bioresorbable. As used herein the term biodegradeable refers to a base polymer that breaks down into oligomeric and/or monomeric units over a period of time, typically hours to months, when implanted or injected into the body of a mammal. As used herein, a bioresorbable polymer is one